Impact of blend properties on die filling during tableting

B. Van Snick[1,2], W. Grymonpré[1], J. Dhondt[3], K. Pandelaere[1], G. Di Pretoro[2], J.P. Remon[1], T. De Beer[3], C. Vervaet[1], V. Vanhoorne[1*]

[1]Laboratory of Pharmaceutical Technology, Department of Pharmaceutics, Ghent University, Ottergemsesteenweg 460, B-9000 Ghent, Belgium

[2]Oral Solid Dosage, Drug Product Development, Pharmaceutical Development and Manufacturing Sciences, Pharmaceutical Research and Development, Division of Janssen Pharmaceutica, Johnson & Johnson, Turnhoutseweg 30, B-2340 Beerse, Belgium

[3]Laboratory of Pharmaceutical Process Analytical Technology, Department of Pharmaceutical Analysis, Ghent University, Ottergemsesteenweg 460, B-9000 Ghent, Belgium

*Corresponding author

Abstract

Based on characterization of a wide range of fillers and APIs, thirty divergent blends were composed and subsequently compressed on a rotary tablet press, varying paddle speed and turret speed. The tablet weight variability was determined of 20 grab samples consisting of each 20 tablets. Additionally, the bulk residence time, ejection force, pre-compression displacement, main compression force, die fill fraction and feed frame fill fraction were determined during each run. Multivariate data analysis was applied to investigate the relation between the process parameters, blend characteristics, product and process responses. Blends with metoprolol tartrate as API showed high ejection forces. This behavior could be linked to the high wall friction value of metoprolol tartrate. The main responses related to the die filling could be predicted via a PLS model based on blend characteristics. Tablet weight variability was highly correlated with the variability on pre-compression displacement and main compression force. A good predictive model for tablet weight variability was obtained taking the porosity, wall friction angle, flowability, density, compressibility and permeability into account. Additionally, turret speed and paddle speed were included in the calibration of the model. The applied approach can save resources (material, time) during early drug product development.

Key words

continuous direct compression

continuous manufacturing

tableting

die filling

blend properties

PLS model

Abbreviations

BRT	bulk residence time
EF	ejection force
FFFF	feed frame fill fraction
PC	principal component
PCA	principal component analysis
PLS	partial least squares
PS	paddle speed
RMF	residence mass feed frame
R^2	Coefficient of determination
R^2X	goodness of fit
Q^2	goodness of prediction
RSD_PCD	residual standard deviation on the pre-compression displacement
RSD_MCF	residual standard deviation on the main compression force
RSD_TW_mean	residual standard deviation on the mean tablet weights of 20 samples
RSD_TW_sample	pooled residual standard deviation on the tablet weight

1 Introduction

Oral solid dosage forms are most used and desirable for drug administration to large populations. Even though alternative drug delivery forms generate significant academic interest, tablets still account for more than 80% of all pharmaceutical products. The popularity of tablets is mainly due to their accurate dosing, ease and low cost of manufacturing, high patient compliance and good chemical and physical stability (Armstrong 2007).

Tablets are manufactured by compressing a powder or granular material in a die and mass production of tablets is performed on high-speed rotary presses. Three distinct steps can be distinguished in the tableting process: filling of materials in the die, compressing the material to a tablet and ejecting the tablet from the die. Current study focused on the die filling step as it is often the rate limiting step of the tableting process. Reproducible die filling is of key importance during tableting as the volumetric filling process implicates that the amount of powder metered in the die dictates the tablet weight and consequently, the drug dose administered to the patient. As consistent and uniform filling of dies is directly linked to the variation in tablet weight and consequently compression force, it could also impact other critical tablet quality attributes as tensile strength, porosity and drug release and eventually even the bioavailability of specific drug products (Armstrong 2007).

The die filling process is governed by multiple mechanisms: gravity, forced feeding in the feed frame, suction fill, centrifugal forces and overhead pressure. The powder flows into the die under the effect of gravity (i.e. gravity feeding) and is thereby assisted by the paddle wheels in the feed frame (i.e. forced feeding). In addition, the rapid downward motion of the lower punch creates a partial vacuum in the die which pulls the powder in the cavity (i.e. suction fill) and the rotation of the turret implicates that centrifugal forces are also present during the die-filling step. Finally, the overhead pressure also contributes to die filling as the powder bed is densified at the inlet of the feed frame due to the pressure induced by the weight of the powder in the feed tube (Peeters et al. 2015, Sinka et al. 2004, Jackson et al. 2007, Schneider

et al. 2007, Xie et al. 2006). After die filling, the amount of powder filled into the die can be reduced when the lower punch moves upwards to eject an excess of powder (i.e. weight adjustment). This weight adjustment step can mitigate non-reproducible die filling as small weight differences are leveled off by removing the excess of powder.

The powder properties and the process parameters affect the die filling step of the tableting process. Powders flow under the applied forces and their flow behavior is dependent on bulk (e.g. density) and particle (e.g. size and shape distribution) properties, environmental conditions (humidity and temperature) and state of the powder (e.g. aerated or dense powder bed) under the applied processing conditions. Previous research focused on characterization of tablet weight variability as a function of paddle wheel and turret speed, but was limited to only a few model formulations (Mendez et al. 2012, Peeters et al. 2015, Sinka et al. 2004, Jackson et al. 2007, Van Snick et al. 2017a). In contrast, current work aims to reveal the impact of both process settings and a wide variety of blend properties on the die-filling step of the tableting process. To address this, a blend property database consisting of divergent blends was composed and these blends were tableted at different process settings. In contrast to previous studies, the blend property database included not only flowability-related descriptors but also descriptors for density, porosity, wall friction angle, permeability and compressibility (Peeters et al. 2015, Jackson et al. 2007, Mendez et al. 2012, Sinka et al. 2004). Finally, partial least squares (PLS) modeling was applied to reveal the impact of blend properties and process settings on tablet properties and tableting process responses.

Current research aims to (1) reveal the correlations between blend properties, process parameters and process and product responses related to die filling and (2) establish a predictive empirical model for prediction of these responses via PLS.

Recently, advanced multivariate modeling strategies (e.g. T-PLS) were reported that aim to link the properties of each raw material, mixing ratios and process conditions with multiple product or process responses (García-Muñoz, García-Muñoz and Polizzi, Polizzi, Tomba). These approaches could enable in-

104 silico formulation development but require large datasets to calibrate all linear and non-linear formulation
105 effects in such a holistic model. Moreover, they rely completely on the availability of characterization
106 results of a relevant lot for the individual raw materials. Therefore, current research established a PLS
107 model that directly links the blend properties (instead of raw material properties and mixing ratios) to the
108 die filling responses. In this research paper, variation in blend properties was induced during calibration
109 through interchanging the active component and/or excipients in tertiary formulations thereby ensuring
110 model robustness towards new formulations. The latter approach is both lean in calibration (no effects of
111 individual materials and composition need to be estimated) and use (it requires only characterization of
112 the blend of interest to predict die filling behavior of any formulation provided the design space boundaries
113 are respected). In drug product development, the model could allow to evaluate the die-filling performance
114 of different characterized formulations of interest (e.g. different platform formulations or varying drug load
115 in a platform formulation). Blend characterization consumes only a limited amount of API compared to high
116 speed compression trials on a rotary tablet press. Therefore, the presented approach could facilitate
117 formulation development during early phases of drug product development when only a limited amount
118 of API is available at high costs and the final dose still needs to be defined.

119 ## 2 Materials

120 Table 1 provides an overview of the investigated materials as well as their brand name, abbreviation,
121 functional class and supplier. The details of API _SD were not provided due to confidentiality reasons.

122 ## 3 Methods

123 ### *3.1 Blend selection*

124 Binary blends composed of an active ingredient and a filler were investigated in a 10/90 weight ratio.
125 Additionally, 1.25% and 0.75% magnesium stearate was added to the blends with mannitol as filler and the
126 other blends, respectively. Thirty divergent blends were selected to correlate the impact of blend

properties with die filling during tableting. The blends were designed to span a wide range of properties by combining 5 DC fillers with 6 APIs. Therefore, these materials were selected based on a database which was developed through extensive characterization of a wide range of materials (Van Snick et al. 2018). Table 2 provides an overview of the studied formulations.

3.2 Raw material and blend characterization

The raw materials included in this study were characterized using the protocols described in a previous publication (Van Snick et al. 2018). As particle properties were not considered relevant for blends, the unlubricated blends were characterized for a subset of these properties: compressibility, density, flowability, permeability, wall friction and porosity. An overview of the included descriptors for these properties and the used equipment is given in Table 3. Additionally, the wall friction of the lubricated blends was determined.

3.3 Blend preparation

3.3.1 Standard blending procedure

First, the actives were screened through a 1400 µm sieve. The active and filler were transferred to a 20 L stainless steel drum which was filled to 60% of its volume. This drum was tumbled (Inversina, Bioengineering, Wald, Switzerland) for 25 min at 15 rpm. Finally, magnesium stearate was added and tumble mixed for 5 min at 15 rpm.

3.3.2 Blending procedure for agglomerated actives

As some active ingredients (paracetamol powder, micronized paracetamol and micronized metoprolol) contained agglomerates, the additional steps described below were added to the standard blending procedure to de-lump the agglomerates and disperse the active uniformly throughout the blend at primary particle level. Therefore, equal amounts of active and filler (50:50 w/w ratio) were tumble mixed for 15 min at 25 rpm. Subsequently, the pre-mix was co-milled through a screen of 1400 µm (U5, Quadro, Canada, Ontario) and tumble mixed an additional 5 min at 25 rpm. Next, the remaining amount of filler was added

to the pre-mix and blended during 15 min at 25 rpm. Finally, magnesium stearate was added and tumble mixed for 5 min at 15 rpm.

3.4 Tableting

3.4.1 Experimental set-up and procedure

The blends were tableted on a Modul™ P rotary tablet press (GEA Pharma Systems, Halle, Belgium). First, the lubricated blend was transferred from the conical hopper to the plexiglass feed tube of the tablet press by means of a rotary valve. A level sensor continuously monitored the height of the powder bed in the feed tube and provided feedback to the rotary valve. When no material was present at the height of the level sensor, the rotary valve refilled the feed tube up to the level of the sensor. This set-up ensured minimal variation in the overhead pressure on the powder bed and mimicked the set-up of a tablet press in a continuous manufacturing system. The tablet press feed frame was equipped with standard curved paddle wheels and ten flat faced Euro B punch pairs (10 mm diameter). The set-up of the tablet press is shown in Figure 1. The tablets were collected on an external balance (K-sampler, Coperion K-Tron, Niederlenz, Switzerland) that logged the weight gain every second. Multi V software (GEA Pharma Systems, Belgium) was installed on the Modul™ P which allowed logging of in-line process responses (pre-compression displacement and force, ejection force) at one-second intervals. The steady state phase of the tableting process was determined during each run based on the powder flow rate through the press (measured using the external balance) and in-line process analyzers logging the pre-compression displacement and main compression force.

The tablet press was operated in a manual mode without active feedback control loop for adjustment of tablet weight or hardness during tableting. Therefore, the fill depth and overfill level were fixed at 8 mm and 2 mm, respectively. For each experiment, the punch positions were adjusted to reach an average pre-compression displacement, pre-compression force and main compression force of 0.5 mm, 2 kN and 15.0 kN, respectively. The speed of the first paddle wheel and turret was varied according to a two-level full

175 factorial screening design of experiments with duplicate center point. Table 4 depicts the experimental
176 conditions and run order in the experimental design. The ratio of the speed of the second over the first
177 paddle wheel was fixed at 1.2.
178 After reaching steady state, twenty grab samples were collected following a pre-defined sampling strategy,
179 i.e. the duration and interval of sampling were adjusted based upon the rotation rate of the turret (Table
180 5).

181 ### *3.4.2 Product responses*

182 #### *3.4.2.1 Tablet weight*

183 The average tablet weight (TW) was included as a response since the tableting process operated in open
184 loop, i.e. fill depth and overfill level were fixed throughout the entire run. This allowed to characterize the
185 intrinsic relation between die filling and blend properties without any impact of controller actions.

186 #### *3.4.2.2 Tablet weight variability*

187 The overall variability in tablet weight can be due to drifts or oscillations in mean tablet weight during
188 processing or to inherent variability in die filling at any random point in the process. To differentiate
189 between these distinct causes of tablet weight variability, the relative standard deviation on the mean
190 tablet weights of the twenty samples (RSD_TW_mean: Equation 1) and their pooled residual standard
191 deviation were calculated (RSD_TW_sample: Equation 2). RSD_TW_mean indicates the variability of the
192 mean tablet weight and consequently provides information on drifts or oscillations during tableting. In
193 contrast, RSD_TW_sample estimates the variability within a random sample.

194 $$RSD\_TW\_mean\ (\%) = 100\ \times \frac{Standard\ deviation\ (mean\ weight\ S1\ ;\ \ldots\ ;\ mean\ weight\ S20)}{Mean\ (mean\ weight\ S1\ ;\ \ldots\ ;\ mean\ weight\ S20)}$$ Equation 1

195 $$RSD\_TW\_sample\ (\%) = 100\ \times \frac{Pooled\ standard\ deviation}{Pooled\ mean}$$ Equation 2

3.4.3 Process responses

3.4.3.1 Die fill fraction

The die fill fraction (DFF) was calculated as the ratio of the actual mass in the die (i.e. tablet weight TW) and the mass calculated from tapped density of a specific blend and the die volume (equation 3). Although the tapped nor bulk density cannot represent the in-situ density in the feed frame, the die fill fraction was not calculated based on the bulk density as this resulted in die fill fractions >1, which is physically impossible.

$$Die\ fill\ fraction\ = \frac{Mean\ tablet\ weight\ (g)}{Tapped\ density\ \left(\frac{g}{mL}\right) \times Die\ volume\ (mL)} \qquad \text{Equation 3}$$

3.4.3.2 Residence mass and fill fraction of the feed frame

The residence mass in the feed frame (RMF) was determined by weighing the residual blend mass in the feed frame after stopping the steady state tableting process. Additionally, the residence volume in the feed frame (RVF) was calculated by normalizing the residence mass in the feed frame based on the tapped density of the formulation using Equation 4:

$$Residence\ volume\ feed\ frame\ (ml) = \frac{residence\ mass\ (g)}{tapped\ density\ (\frac{g}{ml})} \qquad \text{Equation 4}$$

Next, the feed frame fill fraction (FFFF) was calculated as the ratio of the residence volume of the feed frame and the feed frame volume (equation 5).

$$Feed\ frame\ fill\ fraction\ = \frac{Residence\ volume\ feed\ frame\ (mL)}{Feed\ frame\ volume\ (mL)} \qquad \text{Equation 5}$$

3.4.3.3 Bulk residence time in the feed frame

The average flow rate through the press was calculated by multiplying the turret speed with the average amount of blend that was compressed per turret revolution using equation 6.

$$Flow\ rate\ \left(\frac{g}{s}\right) = Turret\ speed\ \left(\frac{revolution}{s}\right) \times\ Tablet\ weight\ \left(\frac{g}{punch}\right) \times\ 10\ \left(\frac{punch}{revolution}\right)$$ Equation 6

Next, the bulk residence time (BRT) in the feed frame of the tablet press was calculated using equation 7:

$$Bulk\ residence\ time\ (s) = \frac{Residence\ mass\ (g)}{Flow\ rate\ \left(\frac{g}{s}\right)}$$ Equation 7

3.4.3.4 Variability on pre-compression displacement and main compression force

The experimental set-up and procedure allowed to assess the suitability of in-line process analyzers for monitoring tablet weight variability throughout the process. The relative standard deviation was calculated for the pre-compression displacement (RSD_PCD) and main compression force (RSD_MCF) signals which were continuously collected during the experiments and statistical analysis was applied across the sampling period.

3.4.4 Multivariate data analysis

Simca 14.1 software (Umetrics, Umea, Sweden) was used for principal component analysis (PCA) and partial least square (PLS) modeling.

4 Results and discussion

4.1 Principal component analysis of blend property database

PCA was applied on the blend property database to reveal how blend properties are related and how blends differ. The principal components (PCs) derived from the PCA model can be considered as overarching properties which represent specific underlying material properties, whereas the loading of the PCA model indicates the importance of properties towards the principal components. Therefore, loading scatter plots were used to assign overarching properties to the respective PCs because descriptors with large positive or negative loadings strongly impact these PCs. In contrast, a descriptor near the origin of the loading scatter plot is not relevant for the respective PCs. In addition, the loading scatter plot visualizes how properties relate to each other by drawing an imaginary line through the property of interest and the origin of the loading scatter plot. Next, any other property can be projected perpendicular on that line to assess their correlation. The properties are positively correlated when the projected property was positioned close to the selected property on the imaginary line. In contrast, the properties are anti-correlated when their projection is located on the opposite side of the straight line. The (anti)-correlation is weaker when the projection is close to the origin of the loading scatter plot.

4.1.1 Summary of fit

Up to 4 PCs were included in the PCA model ("PCA_blends"). For every PC, R^2X and a Q^2 values were calculated (Table 6). R^2X is a quantitative measurement of the goodness of fit (= the explained variation) where 0 and 1 indicate no fit or a perfect fit, respectively. Q^2 is a quantitative measurement of the goodness of prediction, calculated via cross-validation using the default Simca settings. R^2X value converges to 1 when increasing the number of PCs, yet if too many PCs are included in the model, Q^2 decreases due to overfitting. No increase of Q^2 was observed when increasing the number of PCs from three to four. Nonetheless, the 4th PC was retained in the PCA model as a physical meaning could be attributed to this PC (section 4.1.2.4) which included rather unique information.

4.1.2 Loading scatter plot

4.1.2.1 PC1: Flow, cohesion and compressibility-related properties

The first component (R^2X=44 and Q^2=36%) was mainly influenced by flowability, cohesion and compressibility. High positive PC1 loadings were observed for density-weighed flow (ffp and ffrho, Figure 2), powder flow under consolidation (ffc) and flowrate through an orifice (FP). These responses were positively related to the change in permeability per unit of density (k_ρ_sus), signifying that poorly flowing blends will have a higher reduction in permeability (i.e. negative values for k_ρ_sus). The flowability was negatively related to the cohesion (τc, UYS), internal friction (Φ_e and Φ_{sf}) and compressibility (C_15kPa, Cmax). UYS reflects the stress required to initialize the flow of a consolidated mass of material when it is in an unconfined state (i.e. free unstressed surface). This response clustered with C_15kPa, Cmax and τc, indicating these properties describe the intrinsic cohesiveness of a powder. The kinetic constant of the compressibility – pressure relation (i.e. b, the pressure needed to reduce the powder bed volume by 50%) showed moderately positive PC1 loadings. This position suggested that blends with a low compressibility tended to achieve half of their maximal volume reduction at lower pressures. The above-mentioned properties were particularly interesting for PC1 as they all showed relatively neutral loadings for the 2nd PC.

4.1.2.2 PC2: Permeability and density-related properties

The second PC explained 25% and predicted 23% of the variability in the blend property database. The permeability descriptors (k_2kPa and k_15kPa) were located at the bottom center of the PC1 vs PC2 loading scatter plot (Figure 2), whereas the density descriptors (ρtrue, ρb, ρt, CBD, RHOB) clustered in the top right corner. This indicated that air can permeate less easily through a denser powder bed. The plot illustrated also that ρb correlated particularly well with CBD (R^2 = 1.0), confirming the validity of both methodologies. The porosity (ε) was inversely related to the density descriptors, indicating that dense powders generally have a low void fraction. HR and CI clustered together as descriptors of the propensity of powders to be compressed. However, they correlated only moderately with the corresponding descriptors of the FT4

compressibility test (R^2 CI and C_15kPa = 0.6). This discrepancy indicated that the stress levels of both tests were not comparable. The PC1 vs PC2 loading scatter plot suggested that the permeability reduced more per unit of compressibility (%) for highly compressible powders (R^2 CI and k_CI_Sus = 0.50). $\Phi_{lin,}$ and WFA had neutral loadings for both PC1 and PC2.

4.1.2.3 PC3: WFA and ε, Φlin and MPS

The PC3 vs PC4 loading scatter plot indicated strong positive PC3 loadings for WFA (Figure 3). Strong negative PC3 loadings were observed for ε, Φlin and MPS. Blends with a higher MPS have in general a shear stress that is more susceptible to the applied normal stress, i.e. a higher Φlin (R^2=0.82). Furthermore, blends with a high void fraction (ε) tended to have a lower WFA (R^2 = -0.83).

4.1.2.4 PC4: b, k_CI_Sus and permeability

Descriptors k_CI_Sus and b were situated at the top center of the PC3 vs PC4 loading scatter plot (Figure 3). Their correlation (R^2 k_CI_sus and b = 0.63) suggested that blends with high b values suffer generally less from a reduction in permeability per unit increase in compressibility. The permeability-related descriptors (k_15kPa and k_2kPa) were situated in the bottom center of the loading scatter plot.

4.1.3 Score scatter plot

The score scatter plots (Figure 4 and 5) show the relation between different blends based on the score values of their principal components. The blends cluster on the plot if they possess similar values for the descriptors that contribute to the respective PCs. In contrast, the blends are located on different regions of the score scatter plot if they are distinctly different. The score and loading scatter plots were evaluated simultaneously: blends with a specific location (i.e. scores combination) on the score scatter plot possess high values for properties with similar location (i.e. loadings combination) on the loading scatter plot (positive correlation) and low values for properties at the opposite side of the loading scatter plot origin (negative correlation).

The PC1 vs PC2 and PC3 vs PC 4 score scatter plot (Figure 4) show how the blends clustered based on the selected filler which indicated the importance of excipient screening for formulations with a low drug load (10% API). In addition, similar patterns were observed within each filler cluster which highlights that actives can exert even at a 10% drug load a significant impact on blend properties. The PC1 vs PC2 scores plot revealed that blends manufactured with DCP have the highest density followed by T80, 100SD, PH200 and PH101. Blends composed of 100SD and DCP flowed generally best followed by PH200, T80 and PH101. The blends composed of different fillers possessed different score values for both PCs, whereas blends composed of the same filler differed mostly along PC1. Thus, the impact of API properties was more pronounced on the flow (PC1) than on the density of the blend (PC2).

4.1.4 Goodness of fit and prediction of individual properties

Excellent R^2X and Q^2 (>0.9) were obtained for the density measures (i.e. ρb, ρt, CBD and RHOB) as their redundancy ensured good predictive ability during cross-validation (Figure 7). Most techniques related to cohesion, compressibility and flow (UYS, FFc, FFRHO, FFp, ffc, C_15kPa, Cmax, τc, Φe, Φsf, C_15kPa and Cmax) achieved Q^2 above 0.7 because these physical properties are intrinsically related to each other (Figure 7). In contrast, lower predictive performance ($Q^2 < 0.5$) was observed for FP, permeability (k_2kPa, k_15kPa), WFA, Φlin and b as these are rather unique properties. Although excluding these unrelated properties from the PCA would improve the overall predictive performance of the model, it could also jeopardize its ability to distinguish blends that are similar per the first two PCs but differ in such unique properties.

4.2 PLS model to link blend and process parameters with die-filling responses

All blends were processed on the rotary tablet press according to the experimental design presented in Table 4. However, some blends could not be tableted due to capping (F1, F2, F3) or high ejection forces (> 1.2 kN) (F6, F12, F24, F30). Based on the PCA analysis described in section 4.1, several blends (F20, F22, F26, F28 and F29) were only processed at center point settings as blends with similar properties (similar

score values for PC1, PC2, PC3 and PC4) were already characterized and thereby the variation they induce was already enclosed during calibration. Formulations F1, F2 and F3 contained 100SD as filler in combination with a paracetamol grade (P_µ, P_P and P_DP) and exhibited capping which could be attributed to the elastic behavior of paracetamol upon compression (Di Martino et al. 1996, Garekani et al. 2000). Formulations F6, F12, F24 and F30 could not be processed due to excessive ejection forces and included MPT as API in combination with SD100, DCP, T80 and PH200. MPT had the highest WFA (WFA=29.4°) among the APIs included in the study and the corresponding lubricated MPT blends with 100SD, T80, PH200 and DCP also showed the highest WFA (Figure 6). EF correlated well with WFA of the lubricated blends, but a less clear correlation was observed with WFA of unlubricated blends (Figure 6). Generally, WFA of the blends dropped after lubrication. However, WFA of MPT formulations did not decrease after lubrication with DCP, PH101, PH200 and SD100 as fillers. Thus, it appeared that lubrication did not affect WFA of these MPT formulations which could possibly be attributed to the high specific surface area of micronized metoprolol tartrate. In conclusion, lack of processability due to high EF could only be assessed based on lubricated WFA values.

4.2.1 Partial least square regressions

4.2.1.1 Summary of fit

An overall PLS model ("PLS_overall") was constructed to link the blend properties and tableting process parameters with the logged process responses and tablet quality attributes. A model with 3 PCs, explaining each 26%, 22% and 16% of the correlation, respectively, was constructed as inclusion of more PCs did not improve the predictability (Q^2) of the model. The highly-correlated blend properties ($R^2 > 0.98$) CI (R^2 CI and HR: 1.00), FFp (R^2 FFp and FFRHO: 1.00), RHOB (R^2 RHOB and ρb: 0.99), CBD (R^2 Cmax and ρb: 1.00) and k_2kPa (R^2 k_2kPa and k_15kPa: 0.98) were excluded from the PLS model to avoid model distortion. Similarly, a strong correlation between these blend properties was observed by PCA (section 4.1). EF was excluded from the model as it was exclusively linked to WFA. An overview of the goodness of fit (R^2X) and

goodness of prediction (Q^2) of every response in the overall PLS model is shown in Figure 8. High values for R^2X and Q^2 (>0.70) were obtained for BRT, DFF and TW, whereas descriptors related to die filling consistency were more challenging to model. While construction of a sub-model including only poorly flowing formulations (FFc < 4) was not effective to improve R^2X and Q^2, a submodel ("PLS_high_TS") including runs performed at turret speeds of 55 and 100 rpm was successful to improve R^2 and Q^2 for all responses in the model. In the latter model, 3 PCs were included, explaining each 40%, 24% and 10% of the correlation, respectively, and R^2X and Q^2 values of at least 0.77 and 0.65 were obtained for the individual responses (Figure 8). This approach enabled to model the descriptors related to tablet weight variability (RSD_TW_mean: R^2X 0.79, Q^2 0.71 and RSD_TW_sample: R^2X 0.82, Q^2 0.75) which are most critical and relevant to the tableting process. In contrast, the correlation between blend properties, process parameters and tablet weight variability responses was poor when the tablets were manufactured at low turret speeds (10 rpm) as the observed tablet weight variability was consistently low (RSD_TW_mean below 1.2% RSD), irrespective of the blend properties (Figure 9). At low turret speeds, reproducible die filling proved less dependent on the blend properties as more time was available for die filling. In contrast, processing of the blends at higher turret speeds resulted in higher tablet weight variability (RSD_TW_mean up to 4.4% RSD). When less time was available for die-filling, the blend properties had a major impact on the consistency of die filling step and consequently it was more convenient to model tablet weight variability-related responses under such conditions.

4.2.1.2 Loading scatter plots

The loading scatter plots of the PLS models were analyzed to unravel the link between process responses, blend properties and process parameters. Similar correlations were identified on the loading scatter plots of the overall- and sub-PLS model ("PLS_high_TS"). Figure 10 shows the loading scatter plot (PC1 vs PC2) of the PLS_high_TS model: the descriptors for tablet weight variability (RSD_TW_mean, RSD_TW_sample)

clustered together with the variability on the pre-compression displacement (RSD_PCD) and main compression force (RSD_MCF). This proved the validity of the concept on which control loops for adjustment of the tablet weight in rotary tablet presses are based. Interestingly, RSD_TW_mean and RSD_TW_sample clustered closely on the PLS loading scatter plot which indicates that the variability on the mean tablet weight across the run was high when there was a higher weight variability within a grab sample. However, the absolute values observed for RSD_TW_sample were generally higher in comparison to the RSD_TW_mean. The blend properties describing flowability (ffc, FFRHO, FP, UYS, MPS), friction (Φe, Φsf, Φlin), permeability (k_15kPa), compressibility (b, Cmax), cohesion (τc), porosity (ε) and wall friction angle (WFA) highly affected the tablet weight variability. Lower tablet weight variability was obtained for blends with a low porosity, low compressibility, high wall friction angle, high permeability and good flowability. It is generally recognized that low tablet weight variability can be achieved when tableting well flowing materials as these materials flow easily and reproducibly into the die (Mendez et al. 2012, Peeters et al. 2015, Sinka et al. 2001, Sun et al. 2010, Mehrotra et al. 2009, Yaginuma et al. 2007, Van Snick et al. 2017a). However, the permeability, compressibility, wall friction angle and porosity of the blend showed an equally strong influence on tablet weight variability and should therefore also be considered whilst formulating a blend for a direct tableting process. Porous blends were often found to be highly compressible, hence resulting in poor die filling consistency. The effect of WFA on the tablet weight variability was attributed to the observed anti-correlation between porosity and WFA in section 4.1.2.3. Besides these blend properties, the turret speed also exhibited a dominant effect on the tablet weight variability. As less time for die filling was available at higher turret speeds, non-reproducible die filling resulted in high tablet weight variability (Peeters et al. 2015, Mehrotra et al. 2009). Tablet weight was situated opposite to the descriptors for tablet weight variability along the first PC and showed similar scores on the second PC. This implies that high tablet weights were obtained when die filling was reproducible (low tablet weight variability). Additionally, TW was highly influenced by the blend density.

A third cluster of responses, including bulk residence time (BRT), die fill fraction (DFF) and feed frame fill fraction (FFFF) exhibited negative scores along PC1 in combination with positive scores along PC2. This clustering indicated that tableting with a high degree of fill in the feed frame resulted in complete die filling and longer BRT. Considering a fixed volume of the feed frame, it seems physically amenable that a higher filling degree of the feed frame resulted in a longer BRT as more mixing took place when a higher number of particles was present in the fixed volume of the feed frame. A higher FFFF resulted in more complete die-filling (higher DFF) as more particles were available for die filling. The permeability (k_15kPa) showed the strongest influence on the third response cluster. The better the permeation of air through the blend, the more complete the feed frame and the dies were filled and the longer the BRT. Additionally, BRT, DFF and FFFF were influenced by the paddle speed (PS) and turret speed (TS). At high paddle speed and low turret speed, more material was fed in the feed frame by the paddle wheels whilst it was filled at slower pace into the dies, resulting in a high filling degree of the feed frame and the dies and a long BRT. Mixing in the feed frame at a macro- and microscopic level is regulated through BRT which reflects the average mixing time in that unit operation. The macroscopic powder flow in the feed frame is known to be between plug and mixed flow and can be described through a series of continuously stirred tanks with a plug-flow volume fraction (Van Snick et al. 2017b). Additional macroscopic mixing in the feed frame can convert a blend of non-confirming quality (i.e. out of specification for potency) into tablets which meet the potency specifications. Whereas from a raw material tracking and batch definition perspective within a continuous manufacturing system, the macroscopic mixing in the feed frame is preferably as short as possible to minimize intermingling of two distinct material lots. At a microscopic level, a higher BRT maximizes the applied strain in the feed frame which could improve the uniformity of content but reduces the tablet hardness due to overlubrication effects (Van Snick et al. 2017b, Peeters et al. 2016). Interestingly, BRT was inversely related to the tablet weight variability which remains the principal response of any die filling study. In conclusion, whilst formulators and operators optimize the tablet weight variability by finetuning the

paddle wheel speed they should not overlook the potential impact of this parameter on the macro- and micro-mixing effects.

The third PC of the PLS model explained 10 % of the variability in the dataset. All variables and responses showed neutral scores for the third PC, except for TS and BRT with negative and positive loadings for PC3. This highlighted the strong influence of TS on BRT.

4.2.1.3 Score scatter plot

Figure 11 shows the PC1 vs PC2 score scatter plot of the "PLS_high_TS" model: the runs are clearly clustered based on the filler. A similar trend was observed on the PC1 vs PC2 scores plot of the blend property PCA (Figure 4). Along PC1, the position of the runs was mainly determined by the blend cohesion, compressibility, flowability, porosity and effective angle of internal friction as these properties showed the strongest influence on the tablet weight variability descriptors (RSD_TW_mean, RSD_TW_sample, RSD_PCD and RSD_MCF). In addition, density of the blend had a strong impact on tablet weight. Thus, blends with DCP and 100SD showed the highest tablet weight and the lowest tablet weight variability, whereas PH101-based blends had the lowest tablet weight and highest tablet weight variability. In absolute numbers, RSD_TW_mean was below 1.5% for blends based on PH200, T80, 100SD and DCP. In contrast, absolute values for RSD_TW_mean up to 5% were observed for PH101-based blends. It should be noted that the latter filler lacked good flow properties as it was not engineered for direct compression (Van Snick et al. 2018). Tablet weight and tablet weight variability were also influenced by the API included in the formulation. Inclusion of P_DP, an API with low porosity and high density-weighed flow, generally yielded higher tablet weights and lower tablet weight variability. In contrast, tableting of blends with porous and poorly flowing model APIs (P_μ and Mpt_μ) resulted in tablets with lower tablet weight and higher weight variability. All PH101-based formulations showed low tablet weight and relatively high tablet weight variability, independently of the API in the formulation and the applied process parameters. Robustness of the PH101-based formulations towards changes in model API was also concluded based on the PCA blend

447 model. Although this aspect could be attracting to formulators, it should be noted that the tablet weight
448 variability of these formulations was high.
449 Along PC2, the position of the runs was mainly determined by the blend permeability and density. When
450 PH200 and 100 SD were utilized as filler, they generally showed high positive loadings for PC2 as high FFFF
451 and DFF values and relatively long BRTs were observed due to their high permeability. In contrast, DCP-
452 based blends had negative loadings for PC2 as they are characterized by a low permeability and high
453 density, resulting in low FFFF and DFF values and relatively short BRTs.
454 In addition to the blend properties, a dominant effect of TS and a minor effect of PS on the responses were
455 also observed along PC1 and PC2. This is illustrated in Figure 12 for the overall PLS model ("PLS_overall").
456 Within an API-filler combination, experiments performed at low TS (run numbers 1 and 3) showed lower
457 scores along PC1 and higher scores along PC2 in comparison to the runs performed at high TS (run numbers
458 2 and 4) as lower TS resulted in less tablet weight variability, higher TW and longer BRT. The influence of
459 PS on the responses was opposite but less pronounced compared to TS as the position of PS was opposite
460 to TS but closer to the loading scatter plot's origin.
461

462 ### *4.2.2 Discussion on the PLS model*

463 The developed PLS models allowed to gain insight into the correlation between blend properties, process
464 parameters and both process and product responses related to die filling. Moreover, these models will
465 enable prediction of die filling behavior based upon characterized blend properties. This is particularly
466 valuable during the early phases of drug product development when only a limited amount of API is
467 available at high cost. Consequently, performing high speed compression trials on a rotary tablet press is
468 often not feasible due to limited API availability. The established PLS model and identified relation between
469 WFA and EF allow to assess the feasibility of high speed compression during early drug product
470 development phases. Instead of performing API-consuming rotary tableting trials, six blend properties

(compressibility, density, flowability, permeability, porosity and wall friction angle) should be determined to estimate the most critical die filling-related responses (RSD_TW_sample, RSD_TW_mean, TW, BRT) and EF. The model is an endeavor to obtain information on die filling whilst formulating the API in multiple excipient concepts or at multiple drug loads. It is thereby critical that the properties and process conditions of the new formulation fall within the material and process space that is currently covered by the PCA model.

It was also evaluated if similar or improved model predictivity (Q^2) could be obtained by exclusion of non-significant property descriptors. The significance of a descriptor was evaluated based on the coefficient plots of the individual responses (not shown). Figure 8 provides an overview of R^2X and Q^2 of the resulting model ("PLS_reduced"). The following descriptors significantly contributed to the reduced PLS model: ρb, ρt, ρtrue, HR, ε, FFRHO, Φsf, Φe, C_15kPa, k_15kPa and UYS. The Q^2 values of this model indicated a slight but negligible improvement in predictivity of tablet weight (variability)-related descriptors. Although a similar predictive performance was achieved whilst retaining only six blend properties in the model, all characterization methods had to be applied to derive these six descriptors that are mandatory for predicting die filling behavior.

In the future, the accuracy of the established models can be verified using formulations that are currently in late drug product development or in commercial manufacturing. Additionally, the models will be expanded with multicomponent blends including additional excipients (such as disintegrants, binders, flow aids), varying API/excipient ratios, process parameters (such as additional fill depth levels) and equipment settings (such as different paddle wheel designs).

5 Conclusions

Thirty divergent blends were characterized for their properties to construct a blend property database. PCA analysis revealed how these blend properties related to each other and elucidated the impact of the excipient and API on blend properties. Next, a PLS model was constructed to link the blend properties and

applied process parameters with the process and product responses of the die-filling process. Moreover, these PLS models can be used for prediction of die-filling behavior based on the characterization of a formulation for six blend properties without performing any tableting experiments. Therefore, the approach used in current study is a powerful tool to limit consumption of resources in early drug product development.

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